# Fludeoxyglucose F18 Injection [$^{18}$F]FDG
# Diagnostic - For Intravenous Administration

## DESCRIPTION

Fludeoxyglucose F18, (2-deoxy-2[$^{18}$F]fluoro-D-glucose), Injection is an intravenous, diagnostic radiopharmaceutical for Positron Emission Tomography (PET).

[$^{18}$F]FDG is supplied in isotonic saline as a sterile, non-pyrogenic, clear, colorless solution. The pH of [$^{18}$F]FDG is 5.5 - 7.5, and its osmolality at 37$^{o}$C is 300 mOsmol/kg water.

Fludeoxyglucose F18, (2-deoxy-2-[$^{18}$F]fluoro-D-glucose), may be abbreviated [$^{18}$F]FDG. The structural formula for [$^{18}$F]FDG is the following:

Each vial contains at the end of bombardment (EOB) _____ of 2-deoxy-2-[$^{18}$F]fluoro-D-glucose with a specific activity of no less than_____.

Each mL of [$^{18}$F]FDG contains at EOB _____ of 2-deoxy-2-[$^{18}$F]fluoro-D-glucose and 9 mg of sodium chloride.

[$^{18}$F]FDG is produced in an automated radiochemical synthesis unit from cyclotron produced Fluorine F 18. Fluorine F 18 is produced by proton bombardment of enriched [$^{18}$O]water and is bound to 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-$-D-mannopyranose (mannose triflate) under stereo specific $S_N2$

reaction conditions. This renders no carrier added Fludeoxyglucose F 18. The pH is adjusted by passage through an ion retardation resin.

## Physical Characteristics

Fluorine F 18 decays by positron ($+) emission and has a half life of 109.8 minutes. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 1).

Table 1. Principal Emission Data for Fluorine F 18

| Radiation/Emission | % per Disintegration | Mean Energy |
|---|---|---|
| Positron ($+) | 96.73 | 249.8 keV |
| Gamma (±)* | 193.46 | 511.0 keV |

*Produced by positron annihilation
From: Kocher, D.C. "Radioactive Decay Tables" DOE/TIC-11026, 89 (1981).

## External Radiation

The specific gamma ray constant for Fluorine F 18 is 6.0 R/hr/mCi (0.3 Gy/hr/kBq) at 1cm. The half-value layer (HVL) for the 511 keV photons is 4.1 mm lead (Pb). A range of values for the attenuation of radiation results from the interposition of various thicknesses of Pb. The range of attenuation coefficients for this radionuclide is shown in Table 2. For example the interposition of an 8.3 mm thickness of Pb, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

Table 2. Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding

| Shield Thickness (Pb) mm | Coefficient of Attenuation |
|---|---|
| 0 | 0.00 |
| 4.1 | 0.50 |
| 8.3 | 0.25 |
| 13.2 | 0.10 |
| 26.4 | 0.01 |
| 52.8 | 0.001 |

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 3.

## CLINICAL PHARMACOLOGY

### General

[$^{18}$F]FDG, a radiolabeled analog of glucose, rapidly distributes, after intravenous injection, to all organs of the body. After background clearance, peak imaging is at 30-40 minutes after injection.

Table 3. Physical Decay Chart for Fluorine F 18

| Minutes | Fraction Remaining |
|---|---|
| 0* | 1.00 |
| 15 | 0.909 |
| 30 | 0.826 |
| 60 | 0.683 |
| 110 | 0.500 |
| 220 | 0.250 |
| 440 | 0.060 |

*Calibration Time

***Pharmacokinetics***

In 4 normal male volunteers, after an intravenous dose given over 30 seconds, the arterial blood level profile for [$^{18}$F]FDG can be described by a triexponential decay curve. The half-lives for the different distribution and elimination phases are 0.2-0.3 min, 10-13 min (mean ± s.d.; 11.6 ± 1.1 min), and 80-95 min (88 ± 4 min).

Within 33 minutes, a mean of 3.9% of the injected dose can be measured in the urine. Bladder activity two hours after injection indicates that a mean of 20.6% of the injected dose is present. See the Metabolism subsection for additional clearance times.

**Metabolism**

[$^{18}$F]FDG is taken up by cells and phosphorylated to [$^{18}$F]FDG-6-phosphate at a rate proportional to the rate of glucose utilization within a given tissue. [$^{18}$F]FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[$^{18}$F]fluoro-6-phospho-D-mannose [$^{18}$F]FDM-6-phosphate.

[$^{18}$F]FDG contains 2-deoxy-2-chloro-D-glucose (ClDG) as an impurity. Distribution and metabolism of ClDG are presumably similar to that of [$^{18}$F]FDG, and would be expected to result in intracellular formation of 2-doexy-2-chloro-6-phospho-D-glucose (ClDG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (ClDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated, and the resulting compounds, (FDG, FDM, ClDG and ClDM) presumably leave cells by passive diffusion.

FDG and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration; Clearance from the heart may require more than 96 hours. [$^{18}$F]FDG that is not involved in glucose metabolism is excreted unchanged in the urine.

***Pharmacodynamics***

[$^{18}$F]FDG is a glucose analogue which concentrates in cells that rely upon glucose as a primary energy source. Once in the cell it is phosphorylated and can not exit until dephosphorylation has occurred. Regions of "increased [$^{18}$F]FDG uptake" correlate with increased glucose metabolism. Regions of decreased/absent uptake reflect the absence of glucose metabolism. Background activity reflects uptake by normal cells. [$^{18}$F]FDG uptake in inflammatory cells is inconsistent and may be increased, normal or decreased. Whether or not [$^{18}$F]FDG, C1DG, or their metabolites can inhibit glucose metabolism is not known.

**CLINICAL TRIALS**

In a prospective, open label trial, [$^{18}$F]FDG was evaluated in 86 patients with epilepsy. Each patient received a dose of [$^{18}$F]FDG in the range of 185-370 MBq (5-10)mCi. Demographic characteristics of race and gender are not available. The mean age was 16.4 years (range: 4 months - 58 years; of these, 42 patients were <12 years and 16 patients were <2 years old). Patients had a known diagnosis of complete partial epilepsy and were under evaluation as surgical candidates for treatment of their seizure disorder. Seizure foci had been previously identified on ictal EEG's and sphenoidal EEG's. In 16% (14/87) of patients, the pre-[$^{18}$F]FDG findings were confirmed by [$^{18}$F]FDG; 34% (30/87) of patients, FDG scans provided new findings. In 32% (27/87), FDG scans were not definitive. The influence of these findings on surgical outcome, medical management or behavior is not known.

In several other studies comparing [$^{18}$F]FDG scan results to subsphenodial EEG, MRI and/or surgical findings, the degree of hypometabolism corresponded to areas of confirmed epileptogenic foci.

## INDICATIONS AND USAGE

Fludeoxyglucose F 18 Injection ([$^{18}$F]FDG) is indicated in PET (positron emission tomography) for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

Fludeoxyglucose F 18 Injection is not indicated for distinguishing epileptogenic foci from brain tumors or other brain lesions which may cause seizures.

## WARNINGS

None known.

## CONTRAINDICATIONS

None known.

## PRECAUTIONS

### General

[$^{18}$F]FDG uptake may be changed by fasting or by blood sugar changes associated with diabetes mellitus. Blood glucose levels should be stabilized in non-diabetic patients by fasting before [$^{18}$F]FDG injection. Diabetic patients may need stabilization of blood glucose on the day preceding, and on the day of the [$^{18}$F]FDG scan.

Patients should be monitored for arrhythmias and other manifestations of ischemia. [$^{18}$F]FDG, C1DG and their metabolites theoretically could inhibit glucose metabolism. Their ability to potentiate the arrhythmogenic effects of ischemia has not been studied.

The contents of each vial are sterile and non-pyrogenic. To maintain sterility, aseptic technique must be used during all operations involved in the manipulation and administration of [$^{18}$F]FDG.

[$^{18}$F]FDG should be used within 8 hours of the end of synthesis (EOS).

As with any other radioactive material, appropriate shielding should be used to avoid unnecessary radiation exposure to the patient, occupational workers, and other persons.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Studies with [$^{18}$F]FDG have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

**Teratogenic Effects: Pregnancy Category C**

Animal reproduction studies have not been conducted with [$^{18}$F]FDG. It is not known whether [$^{18}$F]FDG can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, [$^{18}$F]FDG should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when [$^{18}$F]FDG is administered to a nursing woman.

**Pediatric Use**

See Clinical Trials section.

## ADVERSE REACTIONS

The [$^{18}$F]FDG safety data base was evaluated for 374 patients. Of these, 245 were male and 105 were female. For 24 patients, gender was not specified. The mean age was 47.8 years (range under 2 to over 65 years). Eighteen patients were between the age of 0 and 2 years; 42 patients were between the ages of 2 and 21 years old; 213 patients were between 21 and 65 years old and 98 patients were not specified. A racial distribution is not available. In this database, adverse drug reactions that required medical intervention were not reported. In a small, 42 patient subset of the 374 patients studied, 4 patients had transient hypotension, 6 had hypo- or hyperglycemia and 3 had transient increases in alkaline phosphatase.

## DOSAGE AND ADMINISTRATION

[$^{18}$F]FDG uptake may be changed by fasting or by blood sugar changes associated with diabetes mellitus. Blood glucose levels should be stabilized in non-diabetic patients by fasting before [$^{18}$F]FDG injection. Diabetic patients may need stabilization of blood glucose on the day preceding and on the day of the [$^{18}$F]FDG scan.

The recommended dose of [$^{18}$F]FDG for an adult (70 kg) is within the range 185-370 (5-10 mCi), intravenous injection. In children doses as low as 2.6 mCi have been given. Optimal dose reductions for children have not been confirmed.

The optimum rate of administration and upper safe dose for [$^{18}$F]FDG have not been established. The time interval between doses of [$^{18}$F]FDG should be long enough to allow substantial decay (physical and biological) of previous administrations.

It is recommended that PET imaging be initiated within 40 minutes of [$^{18}$F]FDG injection.

The final dose for the patient should be calculated using proper decay factors from the time of the EOS, and measured by a suitable radioactivity calibration system before administration. See decay factors in Table 3.

[$^{18}$F]FDG, like other parenteral drug products, should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

Preparations containing particulate matter or discoloration should not be administered. They should be disposed of in a safe manner, in compliance with applicable regulations.

[$^{18}$F]FDG should be stored upright in a lead shielded environment at controlled room temperature.

Aseptic techniques and effective shielding should be employed in withdrawing doses for administration to patients. Waterproof gloves and effective shielding should be worn when handling the product.

**OVERDOSE**

Overdoses of [$^{18}$F]FDG have not been reported. See Radiation Dosimetry Section for related information.

**Radiation Dosimetry**

The estimated absorbed radiation doses to an average human adult (70 kg) from intravenous injection of 185 MBq (5 mCi) and 370 MBq (10 mCi) of [$^{18}$F]FDG are shown is Table 4. These estimates were calculated based on human[1] data and using the data published by the International Commission on Radiological Protection[2] for [$^{18}$F]FDG.

Table 4. Estimated Absorbed Radiation Doses after Intravenous Administration of 2-deoxy-2-[$^{18}$F]fluoro-D-glucose, [$^{18}$F]FDG to a 70 kg patient.

| Organ | mGy/185MBq | rads/5mCi | mGy/370 MBq | rads/10mCi |
|---|---|---|---|---|
| Bladder Wall | 31.45 | 3.15 | 62.90 | 6.29 |
| [1]Bladder* | 11.00 | 1.10 | 22.00 | 2.20 |
| [1]Bladder** | 22.00 | 2.20 | 44.00 | 4.40 |
| Heart | 12.03 | 1.20 | 24.05 | 2.41 |
| Brain | 4.81 | 0.48 | 9.62 | 0.96 |
| Kidneys | 3.88 | 0.39 | 7.77 | 0.78 |
| Uterus | 3.70 | 0.37 | 7.40 | 0.74 |

| | | | | |
|---|---|---|---|---|
| Ovaries | 2.78 | 0.28 | 5.55 | 0.56 |
| Testes | 2.78 | 0.28 | 5.55 | 0.56 |
| Adrenals | 2.59 | 0.26 | 5.18 | 0.52 |
| Small Intestine | 2.40 | 0.24 | 4.81 | 0.48 |
| ULI Wall | 2.40 | 0.24 | 4.81 | 0.48 |
| LLI Wall | 2.96 | 0.30 | 5.92 | 0.59 |
| Stomach Wall | 2.22 | 0.22 | 4.44 | 0.44 |
| Liver | 2.22 | 0.22 | 4.44 | 0.44 |
| Pancreas | 2.22 | 0.22 | 4.44 | 0.44 |
| Spleen | 2.22 | 0.22 | 4.44 | 0.44 |
| Breast | 2.04 | 0.20 | 4.07 | 0.41 |
| Lungs | 2.04 | 0.20 | 4.07 | 0.41 |
| Red Marrow | 2.04 | 0.20 | 4.07 | 0.41 |
| Other Tissue | 2.04 | 0.20 | 4.07 | 0.41 |
| Bone Surfaces | 1.85 | 0.18 | 3.70 | 0.37 |
| Thyroid | 1.79 | 0.18 | 3.59 | 0.36 |

*With void 1 hour after administration **With void 2 hours after administration
The [$^{18}$F]FDG Effective dose equivalent (Adult)[2] is 0.027 mSv/MBq.

[1]Jones, S.C., Alavi, A., Christman, D., Montanez, I., Wolf, A.P., and Reivich, M. (1982). The Radiation Dosimetry of 2-F-18 fluoro-2-deoxy-D-glucose in man. J. Nucl. Med. 23, 613-617.

[2]ICRP Publication 53, Volume 18, No. 1-4, 1987, page 76.

**HOW SUPPLIED**

[$^{18}$F]FDG for intravenous administration is supplied in a.....

NDC: ..... The vial contains _____ of 2-Deoxy-2-[$^{18}$F]fluoro-D-glucose, at end of bombardment, in a volume of ____ of isotonic saline.

[$^{18}$F]FDG has a concentration of radioactivity of _____ and a specific activity of no less than _____ at end of bomdardment.

> Fludeoxyglucose F 18 Injection is a cyclotron-produced radioactive material which is not licensed by the US Nuclear Regulatory Commission. It is licensed by the Illinois Department of Nuclear Safety under the Radioactive Material License #Il-01204-01 and pursuant to 32 Ill. Adm. Code 335.4010

**Storage**

[$^{18}$F]FDG should be stored upright in a lead shielded container at controlled room temperature.

Storage and disposal of [$^{18}$F]FDG should be in accordance with regulations and a general license or its equivalent, of an Agreement State or a Licensing State.

**Expiration Date and Time**

The expiration date and time are provided on the container label. [$^{18}$F]FDG should be used within 8 hours from the time of the end of synthesis.

Caution: Federal Law Prohibits Dispensing Without Prescription

Manufactured by:

Date of Latest Revision